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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/960,143	09/24/2001	Brenda F. Baker	RTS-0266	5066

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EXAMINER	
SCHULTZ, JAMES	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 06/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/960,143	BAKER ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

1. Applicant's supplemental response filed March 24, 2004 has been entered. This response refers to and requests consideration of the arguments submitted November 26, 2003. The response of November 26, 2003 is considered responsive to the restriction requirement mailed September 26, 2003. Applicants' amendment and arguments submitted July 11, 2003, which necessitated the restriction requirement of September 26, 2003, are considered moot in view of the instantly pending amendment and arguments filed November 26, 2003. Rejections and/or objections not reiterated from the previous office action mailed April 8, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. Arguments are responded to first and new rejection set forth last, with the exception of a rejection under 35 U.S.C. § 112 second paragraph, which is made near the beginning because an a fundamental interpretation made there affects the remainder of the action.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Election/Restriction

3. Applicants' election of SEQ ID NO: 58 of claim 28 is acknowledged. Claim 28 as drawn to SEQ ID NOS:41-50, 52-54, 56-61, 63-67, and 69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable

generic or linking claim. Election was made **without** traverse in the paper filed November 26, 2003.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and by dependency claims 2, 4-20, and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 claims "a compound 8 to 50 nucleobases in length...wherein said compound specifically hybridizes with nucleotides 391 through 1639..."

The claim is indefinite because no compound exists that could specifically hybridize with nucleotides 391 through 1639 while simultaneously being no longer than 50 nucleotides long, because such a nucleotide must necessarily be at least 1248 nucleotides long.

This Office action interprets the claim as being drawn to a compound 8 to 50 nucleotides capable of hybridizing to a region within the region of SEQ ID NO: 3 set forth in claim 1.

Response to Claim Rejections - 35 USC § 112

Claims 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of interleukin-8 expression *in vitro*, does not reasonably provide enablement for antisense-mediated inhibition of interleukin-8 expression *in vivo*, or for methods of treating diseases associated with its expression *in vivo*. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is repeated for the same reasons of record as cited in the Office action dated April 8, 2003.

Applicants traverse the instant rejection by asserting that the Office has failed to meet the burden of providing adequate evidence to support the present rejection, and as such, the rejection cannot be properly maintained. Applicants maintain that the burden is on the Office to explain its reasons for the rejection and support the rejection with (1) acceptable evidence, or (2) reasoning which contradicts applicants claim, which must be supported by current literature as a whole. It is asserted that the Office must prove the disclosure requires undue experimentation.

Although these arguments have been fully considered, they are not convincing. Applicants have merely provided a bald assertion that no evidence has been provided, while failing to acknowledge any of the five review articles that were actually cited in the instant rejection. These five review articles were cited in some detail, including quotes referenced by paragraph and page number, which describe the state of the art of antisense-mediated methods of gene inhibition *in vivo* in the previous Office action. All these articles indicate significant unpredictability in the use of antisense oligos *in vivo* (see previous Office action), which applicants have not diputed in any way. It is maintained that plenty of evidence has been provided to doubt applicants claims that the *in vitro* disclosure provided instantly can lead to inhibition and treatment of the whole animal.

Applicants also argue that the instant specification provides numerous examples of the use of the instant invention in cells in culture, which are living organisms, which applicants

suggest constitutes *in vivo* exemplification. In support, applicants submit that the term "*in vivo*" is art recognized to mean a biological or biochemical process occurring within a living organism, while "*in vitro*" means a biological or biochemical process occurring outside a living organism. Applicants argue that they have exemplified methods of determining target inhibition in four different types of cultured cells, and provided methods for screening the effectiveness of *in vivo* targeting of IL-8 and that they are thus enabled for the practice of methods of inhibition of il-8 in cells or whole animals.

As a first note, applicants argument that the term *in vivo* refers to cell lines is inconsistent with the teachings of both the prior art and the specification. Regarding the latter, it is frequently indicated that *in vivo* refers to the whole animal, for example at page 51 line 4, wherein it is taught that dosages may be estimated based on EC_{50}'s found to be effective in "*in vitro* and *in vivo* animal models". Furthermore, applicants are directed to cancerweb's online medical dictionary (attached), where it is indicated that "*in vivo*" means "within the living body". Also from Agrawal (of record), "Microinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379). Thus, applicants' allegation that *in vivo* is "art recognized" to mean a biological or biochemical process occurring within a living organism is overly broad and unsupported.

Furthermore, the real issue being obscured by this argument of definitions is whether these results enable claims encompassing methods of inhibition in the *in vivo* whole animal. It was acknowledged in the previous Office action that applicants are enabled for *in vitro* methods of IL-8 inhibition, which clearly refers to cells in cell culture. Applicants have merely alleged

that the exemplification of methods of determining target inhibition in four different types of cultured cells along with methods for screening the effectiveness of *in vivo* targeting of IL-8 enables said methods for use in whole animals. However, such an allegation does not meet their burden of countering either the evidence cited in the previous Office action from five different review articles or the reasoning that followed which clearly stated why one may not use results from cultured cells to predict what will happen in the whole animal.

Finally, applicants arguments that they are enabled for target inhibition does not address in any way claims 16-20, which are drawn to actual therapeutic treatments using antisense oligos, which must therefore be delivered to the whole animal. Applicants arguments that *in vivo* refers to cell cultures does not enable claims drawn to treatment. Moreover, even if *arguendo* applicants were enabled for methods of inhibiting a target in the whole animal, applicants have not indicated that any treatment would likely result. Therefore, applicants arguments as they pertain to the treatment claims of 16-20 are considered to be unconvincing.

Finally, Applicants assertions that the instant methods can be used in *in vivo* whole animal models based on the teachings of the specification in general is not adopted, because the guidance is generic, applying to virtually any compound. In light of the five review articles citing significant uncertainty in applying antisense methods to *in vivo* whole animal environments, applicants mere assertion that the claimed methods will work in whole animals are not sufficient to overcome the documented unpredictability as set forth previously.

Response to Claim Rejections - 35 USC § 102/103

Claims 1, 2, and 11 are rejected under 35 U.S.C. 102(b) and 103(a) as being anticipated and/or obvious by Blaser et al. (U.S. Patent Number 5,527,678), and is repeated for the same reasons of record as set forth in the Office action mailed April 8, 2003. Claim 11 is newly included here as necessitated by applicants amendment to the claims.

SEQ ID NO: 8 of Blaser et al. possesses 100% identity with residues 358-392, of SEQ ID NO: 3 of the instant application, and would thus specifically hybridize with nucleotides 391 and 392 of il-8 of SEQ ID NO: 3. Although this reference does not specifically teach the inhibition of il-8 as claimed in the present application, the compound meets the structural limitations of applicant's claim language and is thus considered to possess the functional limitation of inhibiting expression, for the same reasons of record as set forth in the Office action mailed April 8, 2003.

Applicants assertion that Blaser does not hybridize with the selected region as amended by applicants is not adopted, because the oligo of Blaser et al. specifically hybridizes with a portion of applicant's claimed sequence as pointed out above, and thus continues to meet the structural limitations as outlined above and cited previously. The rejection is maintained.

Response to Claim Rejections - 35 USC § 102

Claims 1, 2, 4, 5, 8, 9, and 11-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Nyce, J (WO 99/13886), for the same reasons of record as set forth in the Office action

mailed April 8, 2003. Please note that claim 11 is included in this rejection, as necessitated by applicants amendment to the broad claim 1.

Applicants traverse the rejection by asserting that disclosed sequences are not complementary to SEQ ID NO: 3, therefore one would not expect them to specifically hybridize to SEQ ID NO:3. Applicants argue that it has not been shown that the fragments disclosed on page 55, lines 37-60, of the cited reference are capable of hybridizing to 1L-8 of SEQ ID NO:3. Thus, applicants argue that Nyce does not disclose all the elements of the claimed invention, and, therefore, requested to have the rejection withdrawn.

This is not considered convincing, because SEQ ID NO: 1292 of Nyce et al., disclosed on page 55 at lines 37-60 indeed hybridizes to applicants claimed target region of SEQ ID NO: 3, namely at nucleobases 693 to 711, with 100% complementarity. Thus contrary to applicant's assertion, this reference discloses all the elements of applicants' claims as amended, and the rejection is maintained.

Response to Claim Rejections - 35 USC § 103

Claims 1, 2, and 4-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyce et al. in view of Taylor et al., and Baracchini et al., for the same reasons of record as set forth in the Office action mailed April 8, 2003. Applicants' have amended claims 1 and 11, and by dependency, claims 2, 4-10, and 12-15. Claim 11 is newly included here for reasons stated above at the rejection under 35 U.S.C. § 102(b).

However, the amended claims are not considered free of the prior art cited in the previous Office action, because the amendment merely narrows the targeted region to the 3'-untranslated

region (3'-UTR) of SEQ ID NO: 3. The 3'-UTR is a known in the art to be an obvious antisense targeting region, as evidenced by the statement from Baracchini to this effect (see columns 9 and 10). Thus, the combination of references that formed the basis of the rejection under 35 U.S.C. § 103(a) of the previous Office action continue to teach the elements of Applicants' invention as amended, along with the requisite motivation and expectation of success. The rejection has been restated and an explanation of how the previously cited art continues to apply has been provided. The amendment to claim 11 necessitates its inclusion in the instant rejection. Applicants arguments considered relevant to the rejection as stated below are also addressed.

The invention of the above claims is drawn to antisense compounds, their internucleoside linkages, sugar, nucleobase, and 2' modifications, chimeras, and compositions comprising said compounds and pharmaceutically acceptable diluents or delivery systems thereof that target and inhibit the expression of IL-8 of SEQ ID NO: 3.

Nyce et al. teach antisense compounds and methods that target il-8 and inhibit its expression. Furthermore, Nyce et al., teach antisense compounds that *expressly target applicants newly claimed region* as described above said compounds further comprising internucleoside, and nucleobase modifications or compositions comprising said compounds and pharmaceutically acceptable diluents thereof. Nyce et al. do not teach said compounds that comprise sugar or chimeric modifications.

Taylor et al. teaches the inhibition of expression of any protein using a known cDNA sequence to generate antisense oligos that target that and inhibit the expression of that protein.

Baracchini et al. teaches modifications of antisense compounds comprising sugar, nucleobase, 2' modifications, chimeras, and compositions comprising said compounds and

pharmaceutically acceptable diluents or delivery systems thereof. Baracchini et al. also teach targeting specific regions of a gene including the 5'-untranslated, start codon, coding, stop codon, or 3'-untranslated regions, and demonstrate the methods necessary to achieve gene inhibition.

It would have been obvious to one of ordinary skill in the art to modify the sugar component of the antisense sequences of Nyce et al., who expressly teaches modified antisense targeting of applicants claimed region as outlined in the instant rejection under 35 U.S.C. § 102(b). One would have been motivated to modify the sugar component of the oligonucleotide of Nyce et al., because Nyce et al. and Baracchini et al. teach that such modifications increase an antisense compound's cellular uptake, target affinity and resistance to degradation. Finally, one would have a reasonable expectation of success given that Taylor teaches that with software analysis and high affinity oligos, one needs to screen only 3-6 oligos to find one that inhibits its target 66-95%, and since Baracchini et al. teach making modified antisense compounds targeted to distinct regions of a target gene, the steps of which are routine to one of ordinary skill in the art.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Regarding applicants arguments that Nyce et al. does not teach targeting the region of applicants newly claimed target region of SEQ ID NO: 3, these arguments have been addressed at the discussion of the rejection under 35 U.S.C. § 102(b). Applicants' further assert that the motivation to combine must be particularized, and the required evidence cannot be substituted with a generalized scientific goal, as applicants assert the examiner has done in the present case. Applicants state "At no point do the combined references disclose or suggest modified

oligonucleotides that would specifically hybridize with SEQ ID NO:3 and inhibit the expression of human interleukin 8." This is not considered to be convincing, because the compounds of both Nyce et al. and Baracchini et al. are already modified. Since Nyce et al. expressly teaches modified oligos that target applicants' claimed target region, the rejection is centered on whether or not it is obvious to modify the oligos of Nyce et al., not whether the antisense compounds are obvious, because the compounds are anticipated. The particular modified sugar oligos are disclosed as preferred embodiments, and are actually claimed modifications of Baracchini et al. Since Nyce recognized the value of modifying his oligos to resist degradation and prolong bioactivity, and Baracchini teaches that sugar modifications are preferred towards this same end, these elements are considered substitutable one for the other, and the instant combination of references are thus obvious to combine. The rejection is maintained.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 and 103 that form the basis for the rejections under these sections made in this Office action:

> A person shall be entitled to a patent unless –
>
> 102(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> 103(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 and 11 are rejected under 35 U.S.C. 102(e) and 103(a) as being anticipated and/or obvious by Xiao et al.

The claims of the above invention are drawn to antisense compounds 8 to 50 nucleotides in length that specifically hybridizes with and inhibits the expression of human interleukin-8.

SEQ ID NO: 31 of Xiao et al. possesses 100% identity with SEQ ID NO: 58 of the instant application, and would thus specifically hybridize with human interleukin-8. Although this reference does not specifically teach the function of inhibiting applicants' instant human interleukin-8 as claimed in the present application, the above-listed compound meets all the structural limitations as set forth in the instant claims. Because this sequence is substantially identical to applicant's claimed compounds, in the absence of evidence to the contrary said compound is thus considered to possess the functional limitations of specifically hybridizing with and inhibiting the expression of human interleukin-8. Support for this conclusion is drawn from MPEP 2112:

> Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim **but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection**. "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." *In re Best*, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic. Therefore, a 35 U.S.C. 102/103 rejection is appropriate for these types of claims as well as for composition claims. *Emphasis supplied.*

In rejecting the claims of the above under 35 U.S.C. 102 and 103, a prima facie case has been established by the examiner whereby the burden of proof in showing that the claimed compounds are not anticipated by the compound(s) of the prior art as stated lies with the applicant, as per MPEP 2112.01:

> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

Thus, in the absence of evidence to the contrary, the antisense compounds of claims 1-3 and 11 of the instant application are considered anticipated and/or obvious as outlined above.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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